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REVIEW

History of cyclodextrin-based polymers in food and pharmacy: a review

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Abstract

Cyclodextrins are glucose macrocycles whose inclusional capabilities towards non-polar solutes can be modulated with the help of other macrostructures. The incorporation of cyclodextrin moieties into larger structures produces five types of new materials: crosslinked networks, functionalized chains, amphiphilic cyclodextrins, polyrotaxanes and nanocomposites. This review presents crosslinking and grafting to prepare covalently-attached cyclodextrins, and applications in the food and pharmaceutical sectors, from an historical point of view. In food science, applications include debittering of juices, retention of aromas and release of preservatives from packaging. In biomedical science, cyclodextrin polymers are applied classically to drug release, and more recently to gene delivery and regenerative medicine. The remarkable points are: 1) epichlorohydrin and diisocyanates have been extensively used as crosslinkers since the 1960s, but during the last two decades more complex cyclodextrin polymeric structures have been designed. 2) The evolution of cyclodextrin polymers matches that of macromolecular materials with regard to complexity, functionality and capabilities. 3) The use of cyclodextrin polymers as sorbents in the food sector came first, but smart packaging is now an active challenge. Cyclodextrins have also been recently used to design treatments against the coronavirus disease 2019 (COVID-19).

Keywords Cyclodextrin polymers · Crosslinking · Drug delivery · Regenerative medicine · Food packaging

Abbreviations

DNA Deoxyribonucleic acid
NMR Nuclear magnetic resonance

Introduction

In addition to their remarkable capability to establish supramolecular host–guest interactions because of their toroidal shape and non-polar inside (Morin-Crini et al. 2021), cyclodextrins can also be covalently attached in different ways to generate more complex structures (Řezanka 2019). Materials containing more than two covalently linked cyclodextrin units are known as cyclodextrin polymers, and their uses in the field of remediation technologies have been widely explored (Landy et al. 2012). In the case of drug delivery, the most frequently investigated subject among the biomedical applications, the complexation capabilities of cyclodextrins and the controlled release rate of the guest drugs can be modulated with the aid of the additional functionality of a polymeric macrostructure. In other cases, the covalent attachment of cyclodextrin moieties to a pre-existing structure is intended to immobilize them, as in the case of medical devices or packaging applications.

This review covers, from a historical point of view, the applications both in food chemistry and pharmaceutics and biomedicine of cyclodextrin polymers (see Fig. 1). In contrast to the enormous amount of studies on the uses of the parent cyclodextrins in these two sectors, cyclodextrin polymer references are not as abundant and most of the examples found in the literature correspond to the last 10–15 years.

We can define cyclodextrin polymers as those materials or molecules containing more than two covalently linked cyclodextrin units. Thus, we will not cover in the following

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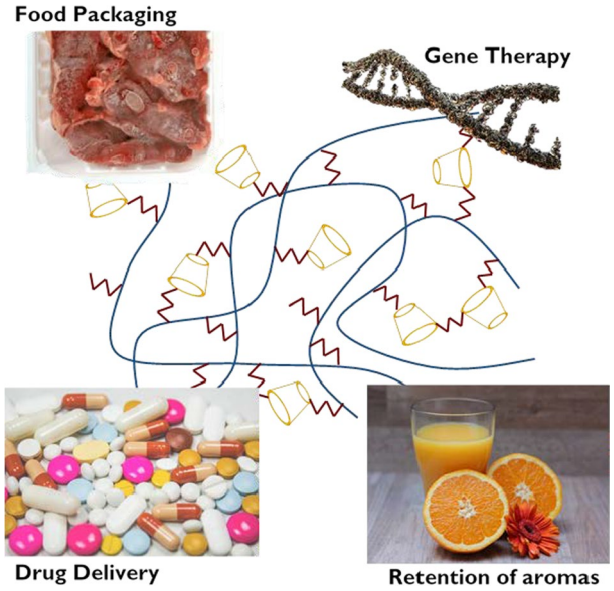

Fig. 1 Uses of cyclodextrin polymers in the food and pharmaceutical sectors

sections of this review either the functionalization of non-polymeric supports, known as cyclodextrin nanocomposites, or the amphiphilic cyclodextrins and star polymers with a cyclodextrin core, or the cyclodextrins threaded onto polymer chains, known as polyrotaxanes.

The first references dealing with the potential use of cyclodextrin-containing covalent structures as macromolecular carriers, date back to the 1980s. Since then, they have been incorporated into many constructions, such as hydrogels, nanosponges, dendrimers, interpenetrating networks, molecular imprinted polymers or electrospinned fibres. In addition, some of these systems have proved to be responsive to stimuli, leading to the design of smart multifunctional biomaterials that can be triggered by different factors. This article is an abridged and updated version of the chapter published by Petitjean et al. (2020) in the series Environmental Chemistry for a Sustainable World.

Cyclodextrin polymers

Historical perspective of cyclodextrin polymers

The pioneering work of Solms and Egli in 1965 can be considered as the first landmark in the field of cyclodextrin polymers (Solms and Egli 1965). Also in those early years, Wiedenhof et al. (1969) improved the properties of the irregular crosslinked cyclodextrin particles and produced bead microparticles that, for instance, were suitable to be used in chromatographic columns.

Polyurethane cyclodextrin networks were prepared using diisocyanates by Buckler et al. (1969). Acid dihalides and many other potentially useful space arms were also considered in the same patent and various possible applications of those "anchored" cyclodextrins were explored.

A few years after that, in the mid-1970s, the first cyclodextrin monomers were produced and polymerized by Furue et al. (1975). This acrylic polymer exhibited a greater catalytic effect in the hydrolysis of *p*-nitrophenyl esters due to the "cooperative effect" between two neighbouring cyclodextrin moieties on a polymeric chain (Harada et al. 1977) (Fig. 2).

The next type of cyclodextrin polymers in our classification corresponds to the attachment of cyclodextrin moieties to previously existing macromolecular materials. In this case, Szejtli, Fenyvesi et al. attached cyclodextrin units to polyvinyl alcohol using epichlorohydrin and epoxy ethers in the late 1970s (Szetjli et al. 1979). Hirayama et al. (1984) used epichlorohydrin to prepare a β-cyclodextrin/starch composite gel. In the 1990s, Pöpping and Deratani (1992) reported the production of

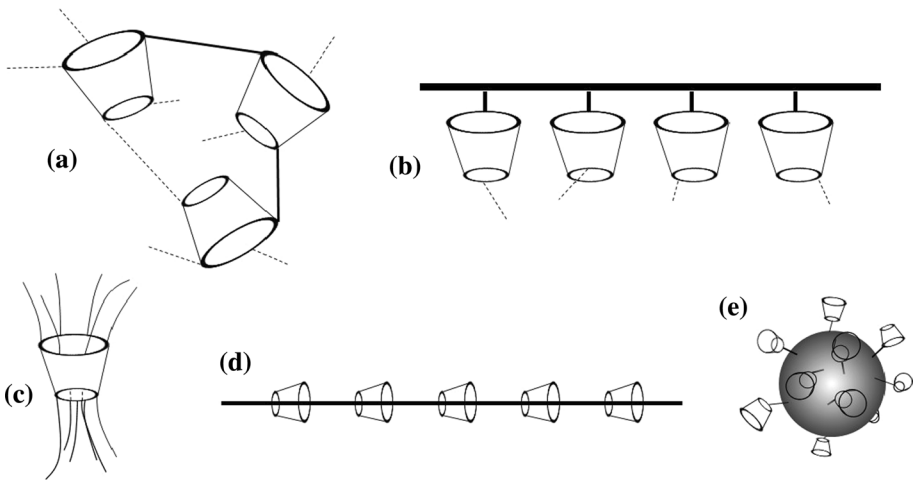

Fig. 2 Cyclodextrin-containing macromolecular systems: **a** crosslinked cyclodextrin polymers (more than three units); **b** linear polymers, either grafted-cyclodextrin polymers or monomeric cyclodextrin (co) polymers; **c** amphiphilic and star-like unimeric cyclodextrins; **d** (pseudo)polyrotaxanes; **e** nanocomposites and immobilized cyclodextrins. Only the first two types of structures are covered in this review

monochlorinated cyclodextrins and, later on, other derivatives containing heterocycles were synthesized (Reuscher et al. 1998). Earlier, in 1981, Tanaka et al. had immobilized derivatives of α- and β-cyclodextrin on polyurethane and also onto a polyacrylamide support after activating it with succinyl hydrazide (Tanaka et al. 1981, 1982) with the aim of obtaining stationary phases for the separation of benzene derivatives. About twenty years ago, Crini et al. used cyclodextrin tosyl derivatives to produce macroporous polyamines (1998a) or to modify polyethyleneimines in order to coat silica beads (Crini et al. 1995). Cyclodextrin side chain polyesters were also obtained in those years (Weickenmeier and Wenz 1996). Wenz et al. also reported the synthesis of thickeners based on the specific interaction between cyclodextrin polymers and guest polymers (Weickenmeier and Wenz 1996).

A comprehensive collection of the first polymers can be found in the review of cyclodextrin-containing adsorbents by Crini and Morcellet (2002). In the last two decades, more complex cyclodextrin polymer structures have been produced, namely interpenetrated networks, molecular imprinted polymers, dendrimers, nanogels, polymer assemblies, and nanocomposites. The especial cases of the feasible uses of these materials in these two sectors will be the goal of the last section of this review.

Covalent and supramolecular architectures

Cyclodextrins crosslinked in covalent networks

Cyclodextrin crosslinked with epichlorohydrin polymers, the most abundant in the literature, were also the first type known, synthesized by Solms and Egli (1965). The reaction of saccharides such as glucose with epichlorohydrin is well known (Dumitriu 1996), and the primary product of the reaction of β-cyclodextrin with epichlorohydrin in alkaline media is a heterogeneous mixture of several ethers, of low molecular weight and viscosity, soluble in water. In this reaction, the self-polymerisation of epichlorohydrin, which is favoured at high temperatures, can also occur (Renard et al. 1997).

The bulk synthesis procedure of Solms and Egli (1965) produced irregular polymer particles. A few years after that, Wiedenhof et al. (1969) proposed a two-phase emulsion polymerisation with controlled stirring, in which the cyclodextrin dissolved in water is dispersed in a non-polar organic solvent containing a non-ionic surfactant and the crosslinker in order to produce uniform microspheres, or beads, with better physicochemical properties. As potential drug delivery devices, cyclodextrin–epichlorohydrin hydrogels made with a controlled geometry are useful to obtain kinetic parameters (Machín et al. 2012).

Among the most frequently used non-epoxide crosslinkers are diisocyanates, first introduced by Buckler et al. (1969), as mentioned above. Dihalogenated acid dihalides or dihalogenated dicarboxylic acids of different sizes have also been used as space arms (Buckler et al. 1969; Zemel and Koch 1990), besides other agents such as dihalogenated alkenes or, later on, maleic anhydride (Girek et al. 2000). Shono et al. prepared insoluble porous polymers with a high cyclodextrin content, polymerising α- and β-cyclodextrin with diisocyanates as crosslinking agents in pyridine or dimethylformamide, and studied their capability to absorb aromatic derivatives (Mizobuchi et al. 1980; Tanaka et al. 1981). Certain properties and applications have been studied thereof: stationary phases in chromatography (Lee et al. 2002); artificial cholesterol receptors (Asanuma et al. 1998); solid phase for the extraction of carcinogenic aromatic compounds (Bhaskar et al. 2004). Ma's group, which also used these two diisocyanates, postulated the presence of interconnected nanoporosity in these polymers (Li and Ma 1999; Ma and Li 1999). The use of difunctional crosslinkers with longer spacers can lead to macromolecular networks with increased porosity, more flexible and less compact. In these networks, smaller molecules can increase their diffusion rates and bulkier substances may also become entrapped (Mocanu et al. 2001). The use of non-toxic crosslinkers like the polycarboxylic acids is also feasible. Martel's group described the synthesis of soluble and insoluble polymers (Martel et al. 2005) and the production of cotton-bound cyclodextrin using these crosslinkers (Martel et al. 2002).

The analysis of cyclodextrin polymers crosslinked with epichlorohydrin is complicated when it comes to infrared or Raman spectroscopic techniques (Crini et al. 2000) because, as mentioned above, both the crosslinked cyclodextrin units and the self-polymerised epichlorohydrin possess hydroxyalkyl and ether groups. Nevertheless, the interpretation of the infrared spectra of starch crosslinked with epichlorohydrin was resolved at the time (Dumoulin et al. 1998; Delval et al. 2004).

While the spectroscopic characterization of cyclodextrin–epichlorohydrin polymers is not easy, that of cyclodextrin polymers crosslinked with diisocyanates seemed to be simpler. Qualitative characterizations by infrared spectroscopy (Li and Ma 1999; Bhaskar et al. 2004) or Raman (Lee et al. 2002) were attempted, and the successful quantitative analysis was achieved thanks to the intense carbonyl band of the crosslinker (García-Zubiri 2005). Thermal and thermogravimetric analysis were also used in most of those studies, as well as NMR spectroscopy (Asanuma et al. 1998; Lee et al. 2002). For polymers with other crosslinkers, such as maleic anhydride, there were also some NMR results of interest (Girek et al. 2000).

As for the cyclodextrin content of the polymer, the most common procedures used already in the 1990s were the

colorimetric methods using chlorotetrazolium blue (Crini et al. 1995; 1998b; Janus et al. 1999) or iodometry (Renard et al. 1997) and phenolphthalein (Mäkelä et al. 1987). For soluble cyclodextrin polymers, proton nuclear magnetic resonance spectroscopy could be used (Renard et al. 1997), and for the insoluble resins ^{1}H or ^{13}C solid-state NMR were employed (Crini et al. 1998b; 2000).

Another technique used to determine the cyclodextrin content in the polymers is CHN elemental analysis (Lee et al. 2002). Nevertheless, it must be used with great care in the case of cyclodextrin–epichlorohydrin polymers due to the similar elemental composition of both constituents (Romo et al. 2006). Important advances in this area have been achieved along the years but the precise characterization of cyclodextrin polymers continues being a challenge as occurs in any other macromolecular materials.

Other novel cyclodextrin polymers

The reticulated cyclodextrins, also known as nanosponges, have evolved into more complex structures in the last 10–20 years (Caldera et al. 2017). Thus, molecular imprinted polymers using cyclodextrin moieties were already produced in the late 1990s (Piletsky et al. 1998). Stimuli responsive polymers based on cyclodextrins were prepared in 1995 using the ubiquitous N-isopropylacrylamide monomer (Nozaki et al. 1995). Interpenetrated networks containing cyclodextrins also appeared at that time (Sreenivasan 1997). Fenyvesi et al. encapsulated several cationic disinfectant agents, in chemically modified (carboxymethylated) nanosponges, based on cyclodextrin linked to polyvinyl alcohol, to be used in the prolonged treatment of wounds (1996).

Nanogels combine the advantages of hydrogels and nanoparticles into a single carrier (Moya-Ortega et al. 2012). Liu et al. prepared cyclodextrin microgels, including one interpenetrated network, by inverse-emulsion polymerisation (2004). About ten years ago, nanoparticles were synthesized by a one-step condensation polymerisation of β-cyclodextrin, choline chloride and epichlorohydrin by Gil et al. (2009). The top-down approach can break bigger networks into the nanoscale size by using ultrasounds (Swaminathan et al. 2010). The water-in-oil emulsion method has been thoroughly employed in the last decade, but their direct synthesis by polymerisation of cyclodextrin monomers is more rare (Moya-Ortega et al. 2012).

Another interesting method of producing nanogels was designed by Gref et al. and consist on supramolecular nanoassemblies between a cyclodextrin–epichlorohydrin polymer and an alkyl-grafted dextran (Gref et al. 2006). Other potential uses of cyclodextrins as 'smart' components of polymer nanoparticles were reviewed by Gref and Duchêne (2012). A variety of cyclodextrin-based architectures, e.g. linear, dendrimers, stars, polyrotaxanes, were used in the preparation of polyplexes for gene delivery (Mellet et al. 2011). In 1997, β-cyclodextrin was attached to dendrimer polyethyleneimines (Suh et al. 1997). Two years later, linear cationic alternate copolymers capable of binding DNA with transfection efficiency were prepared by Davis' group (Gonzalez et al. 1999). Later on, Choi et al. prepared polyplexes grafting cyclodextrin to poly-L-lysine instead of using poly(ethyleneimine) (2005).

Electrospun nanofibres have been used as drug delivery materials due to their high specific area and, obviously, various formulations including cyclodextrins have been tested in the last 5 years (Costoya et al. 2017). Cyclodextrin polymers have been also explored as components of electrospun nanofibres recently (Oliveira et al. 2015). As shown in this short account of the major findings in this field, the evolution of cyclodextrin polymers goes in parallel with the progress in the production of novel macromolecular materials with more complex structures and morphologies, controlled or 'smart' behaviours, and specific applications.

Applications in the food and pharmaceutical areas

Cyclodextrin polymers in food science

In the food industry, cyclodextrins have been applied as sorption/release agents and for packaging purposes (Sarkar et al. 2017). They can be used as single cyclodextrins incorporated into fibres (Celebioglu et al. 2018) or films (Plackett et al. 2006). Crosslinked cyclodextrins were firstly proposed for food related applications as early as the 60s with the patent of Bucker et al. (1969) as agents for concentration of flavours or aromas in the food industry.

Cyclodextrin–epichlorohydrin polymers were developed to reduce the bitterness of fruit juices (Shaw et al. 1984), and a selectivity study between bitter molecules and caffeine was tested (Shaw and Buslig 1986), using γ-cyclodextrin polymer as well. It was proved that cyclodextrin polymers do not complex with the latter and studied the importance of the crosslinking agent.

For the same application, β- or γ-cyclodextrin was linked to chitosan through succinyl or maleyl bridges to improve the sorption of bitter compounds (Binello et al. 2004). Thanks to a pilot-plant fluidised-bed procedure, Wagner successes a regeneration of β-cyclodextrin polymer over twenty times without apparent loss of capacity (1988). The debittering of other juices has also been reported later (Szejtli and Szente 2005).

In the last decade, another area of application searched in food science and cosmetics is the retention of fragrance or aroma molecules. Encapsulation of linalool and camphor, composing *Lavandula angustifolia* essential oil, using

crosslinked cyclodextrin–epichlorohydrin polymers was compared to those of the parent and derivative cyclodextrins (Ciobanu et al. 2012). To absorb unwanted molecules present in wine, beads produced using epichlorohydrin (Fliszár-Nyúl et al. 2020) or hexamethylene diisocyanate can be used (Dang et al. 2020).

In 2009, cyclodextrin polymers were used in solid phase extractions to determine additives in food (Li et al. 2009). In parallel, molecular imprinted cyclodextrin polymers were prepared using monomeric cyclodextrin/maleic acid with Congo Red as template and N,N′-methylenebisacrylamide as crosslinker (Liu et al. 2015). Also, a cyclodextrin polymer with a higher specific area has been prepared (Li et al. 2018), grafted onto metallic graphene (Li et al. 2016a), added to ionic liquids (Feng et al. 2015), or imprinted on carbon nanotubes (Liang et al. 2019), in order to remove and/or determine the amount of organic molecules present in food.

Single cyclodextrins are also common for food packaging; they began to be exploited for that purpose at the end of the past century (Szente and Fenyvesi 2018). The first reported use of a cyclodextrin polymer in packaging was to remove an undesirable product in food such as cholesterol (López-De-Dicastillo et al. 2011).

On the other hand, active films are designed to liberate chemicals encapsulated in them using UV stimuli (Tan et al. 2016). To achieve an antibacterial potential, it is also feasible to integrate ZnO nanoparticles into polymer films (Andrade-Del Olmo et al. 2019) or to crosslink a sorbate/cyclodextrin complex, such that with sodium benzoate (Yang et al. 2019). Starting with the applications to extract unwanted molecules from food products several decades ago, the modern uses of cyclodextrin polymers focus also on smart packaging.

Cyclodextrin polymers in drug delivery

The first reviewing of the potential applications of cyclodextrin polymers in the pharmaceutical industry was written by Fenyvesi (1988), and it was mainly based on cyclodextrin crosslinked with epichlorohydrin. A pioneering bioavailability study using a soluble cyclodextrin polymer was reported in the mid-1980s (Uekama et al. 1985). The absorption-promoting effect of the soluble cyclodextrin polymer on the sublingual route was also demonstrated in the case of steroids (Pitha et al. 1986). Karadake et al. (1982) showed that the drug release was retarded and the stability against oxidation and degradation was greatly increased when penicillin complexed with soluble cyclodextrin polymer was microencapsulated.

On the other hand, some applications of the insoluble crosslinked cyclodextrin polymers were also investigated. For instance, its effect on wound healing was tried on tissues of rats (Felméray et al. 1996). In addition, the cyclodextrin–epichlorohydrin sorption capabilities were tested for the removal of phenylalanine from a protein hydrolysate in order to make it digestible for children suffering from phenylketonuria (Specht et al. 1981). Also at that time, the effectiveness of a cyclodextrin polymer as a tablet disintegrant was studied in direct compression systems (Fenyvesi et al. 1984).

Those first attempts to show their capabilities in the sorption and release of aromatic model molecules pointed to the use of cyclodextrin polymers as controlled release agents (Friedman et al. 1989). Specifically, the release of cetylpyridinium chloride, an antimicrobial agent, and iodine, using cyclodextrin polymers, were patented in the late 1980s (Friedman 1988; Szejtli et al. 1988). An earlier example of a cyclodextrin polymer as a macromolecular carrier in the field of antitumor chemotherapy was published also in the mid-1980s (Kaji et al. 1985).

The following decade showed only a few other distinct examples in drug delivery. Thus, drugs complexed in cyclodextrin polymers were entrapped into liposomes (McCormack and Gregoriadis 1994). On the other hand, the need to prepare degradable materials for medical applications, including drug delivery, associating networks using cyclodextrin–epichlorohydrin polymers and degradable copolyesters containing adamantyl groups were tested and were shown to be pH sensitive (Cammas et al. 1999).

Cyclodextrin-based nanosponges have been designed in the last years to increase the dissolution rate, the solubility and stability of drugs, or to prolong the release time, and also applied in semisolid formulations for skin delivery (Ansari et al. 2011; Shende et al. 2013; Conte et al. 2014). Recently, experimental design has been used to formulate tablets using polymeric nanosponges for a combination therapy of three anti-inflammatory drugs (Moin et al. 2020).

As mentioned above, cyclodextrin moieties can be incorporated to pre-existing polymeric materials via grafting reactions. In most of the drug delivery applications, cyclodextrins are attached to polysaccharides (Luzardo-Alvarez et al. 2014), such as chitosan, for which the adsorption and release of ketoprofen, a model drug, was evaluated some time ago (Prabaharan and Mano 2005). Although cyclodextrin adds new drug inclusional properties to the polycationic polymer, a decrease in mucoadhesion of cyclodextrin-chitosan was observed (Venter et al. 2006). More recently, cellulosic substrates were grafted by a cyclodextrin polymer to sustain the release of antibacterial agents (Cusola et al. 2013). Other materials such as poly(hydroxyethylmethacrylate) have also been grafted with β-cyclodextrin for its application in soft contact lenses conservation liquids and to sustain drug delivery in the lacrimal fluid (dos Santos et al. 2009). The use of some cyclodextrin polymers for therapeutics delivery was patented in 2013 (Cheng et al. 2013).

In the turn of the century, a new class of polymers for the delivery of macromolecular therapeutics arose (Gonzalez et al. 1999). Thus, low molecular weight polyethylenimine crosslinked by cyclodextrins demonstrated its lower cytotoxicity and higher transfection efficiency for the delivery of plasmid DNA compared with those of polyethylenimine (Huang et al. 2006). Another significant achievement has been, for instance, the use of a specific functional group such as folic acid grafted to polyethyleneimine-cyclodextrin carriers, to target the tumour cells (Yao et al. 2009). Intranasal mRNA vaccination with the aid of a cationic cyclodextrin-polyethyleneimine conjugate, capable of overcoming the nasal epithelial barrier, has also been recently proposed (Li et al. 2016b).

Drug release behaviour can be modulated with the aid of stimuli responsive polymers and the design of interpenetrated networks (interpenetrated network) permits to combine the temperature responsiveness of poly(N-isopropylamide) gels with the inclusional capabilities of cyclodextrin networks (Zhang et al. 2005). Another semi-interpenetrated network was prepared by the radical polymerisation and crosslinking of N-isopropylacrylamide in the presence of β-cyclodextrin-grafted polyethylenimine (Zhang et al. 2008). Interpenetrated networks can also be used to develop new selective and synergistic sorption capacities for specific purposes such as a combined drug release (Fujiyoshi et al. 2019).

A remarkable pH-responsive behaviour can be achieved using acrylic acid containing polymers (Siemoneit et al. 2006). Other examples have been reported in the recent literature: highly pH-dependent swelling in graft cyclodextrin/acrylic acid copolymers for the delivery of ketoprofen (Wang et al. 2009), or mucoadhesive hydrogels by the crosslinking of poly(acrylic acid) with cyclodextrins for the controlled release of diflunisal and fluconazole (Kutyła et al. 2013). A biocompatible system based on guar gum, poly(acrylic acid) and β-cyclodextrin using a non-toxic crosslinker, tetraethyl orthosilicate, for intestinal delivery of dexamethasone, has also been reported (Das and Subuddhi 2015). A combination of cocktail chemotherapy, photothermal therapy and inhibition of angiogenesis was investigated using an injectable nanocarrier developed by functionalization of carbon nanotubes with a pH a thermoresponsive cyclodextrin polymer (Das et al. 2020).

In the last decade, triple-response (pH, temperature, and glucose) semi-interpenetrated hydrogels were prepared by polymerisation in the presence of the magnetite (Fe_3O_4) nanoparticles, a cyclodextrin/epichlorohydrin polymer and a crosslinker (Huang et al. 2012). More recently, a carboxymethyl-β-cyclodextrin polymer was grafted on the surface of chitosan-coated magnetite nanoparticles by an emulsion chemical crosslinking method (Ding et al. 2015).

Finally, cyclodextrin polymers have also recently found applications in the field of regenerative medicine (Alvarez-Lorenzo et al. 2017). Vascular polyester and polyamide prostheses can be coated with grafted cyclodextrins that can be loaded with an antibiotic in order to reduce the risk of post-operative infections (Blanchemain et al. 2005). Polyvinylidene difluoride membranes can also be grafted with cyclodextrins to improve the capture and subsequent release of antiseptic agents (Tabary et al. 2007). Polyamide inguinal meshes (El Ghoul et al. 2008) or polypropylene abdominal wall implants for the prolonged delivery of ciprofloxacin (Laurent et al. 2011) have been prepared using citric acid as a crosslinker. Hydroxyapatite used in bone implants can also be functionalized with a cyclodextrin polymer for loading antibiotics (Hoang Thi et al. 2010; Taha et al. 2014). Recently, injectable hydrogels of polyelectrolyte complexes between chitosan and cyclodextrin polymers have been rheologically tested (Palomino-Durand et al. 2019).

As in the case of 'monomeric' both natural and derivative cyclodextrins, an increasing number of publications can be found in the most recent literature concerning cyclodextrin polymers, e.g. about 80 papers and reviews in 2020. As Table 1 shows, many reviews have been published in the last six years, and the interested reader is referred to them to acquire a better idea of the goals this field of research is heading and the paths, or approaches, taken. In addition, some other recent reviews also include a section on cyclodextrin-based systems (Larrañeta et al. 2018; Levack et al. 2018; Solanki et al. 2018; Gim et al. 2019). Cyclodextrins have also been recently used to design treatments against the coronavirus disease 2019 (COVID-19) (Carrouel et al. 2020; Ergoren et al. 2020; Sofiane et al. 2020; Szente et al. 2021).

Conclusion

Immobilized cyclodextrins were first used in the food industry to improve taste, extract some nutrients or flavours, or, more recently, as constituents of the smart packaging of comestible products. The capabilities of the parent and modified cyclodextrins as carriers of substances of low solubility, such as most drugs, were soon exploited for pharmaceutical applications as well. Although the research involving these polymers in the food sector is comparatively scarce, the potential uses in the pharmaceutical and medical sector have been thoroughly investigated, especially in the last decade. A

Table 1 Recent reviews (2015–2021) on the applications of cyclodextrins and cyclodextrin polymers in pharmacy and biomedicine

Authors and year	Review title
Simões et al. (2015)	Supramolecular cyclodextrin-based drug nanocarriers
Osmani et al. (2015)	Cyclodextrin-based nanosponges: Impending carters in drug delivery and nanotherapeutics
Wei and Yu (2015)	Cyclodextrin-functionalized polymers as drug carriers for cancer therapy
Gidwani and Vyas (2015)	A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anti-cancer drugs
Gonzalez-Gaitano et al. (2016)	Drug carrier systems based on cyclodextrin supramolecular assemblies and polymers: present and perspectives
Mejia-Ariza et al. (2017)	Cyclodextrin-based supramolecular nanoparticles for biomedical applications
Peng et al. (2017)	Polymeric nanocarriers based on cyclodextrins for drug delivery: host–guest interaction as stimuli responsive linker
Adeoye and Cabral-Marques (2017)	Cyclodextrin nanosystems in oral drug delivery: A mini review
Alvarez-Lorenzo et al. (2017)	Cyclodextrins as versatile building blocks for regenerative medicine
Fenyvesi et al. (2019)	Applications of steroid drugs entrapped in cyclodextrins
Topuz and Uyar (2019)	Electrospinning of cyclodextrin functional nanofibres for drug delivery applications
Yao et al. (2019)	Cyclodextrin-based polymer materials: From controlled synthesis to applications
Zhang et al. (2019)	Cyclodextrin-based delivery systems for cancer treatment
Ciesielska et al. (2020)	Biomedical application of cyclodextrin polymers crosslinked via dianhydrides of carboxylic acids
Haley et al. (2020)	Cyclodextrins in drug delivery: applications in gene and combination therapy
Qie et al. (2020)	Advances in cyclodextrin polymers and their applications in biomedicine
Seidi et al. (2020)	Polycyclodextrins: synthesis, functionalization, and applications
Tian et al. (2020a)	Cyclodextrin-based delivery systems for chemotherapeutic anticancer drugs: a review
Tian et al. (2020b)	Cyclodextrin as a magic switch in covalent and non-covalent anticancer drug release systems
Wankar et al. (2020)	Recent advances in host–guest self-assembled cyclodextrin carriers: implications for responsive drug delivery and biomedical engineering
Sofiane et al. (2020)	The use of cyclodextrin or its complexes as a potential treatment against the 2019 novel coronavirus: a mini-review

vast amount of papers are currently being published in order to explore the applicability of these interesting materials.

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